

Maximal fluctuations of confined actomyosin gels: dynamics of the cell nucleus

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We investigate the effect of stress fluctuations on the stochastic dynamics of an inclusion embedded in a viscous gel. We show that, in non-equilibrium systems, stress fluctuations give rise to an effective attraction towards the boundaries of the confining domain, which is reminiscent of an active Casimir effect. We apply our result to the dynamics of deformations of the cell nucleus and we demonstrate the appearance of a fluctuation maximum at a critical level of activity, in agreement with recent experiments (Makhija et al., 2015).

There has been growing interest in the role of intracellular mechanical fluctuations on cell behavior, with several recent studies showing that stem cells and cancer cells display higher fluctuation levels than normal differentiated cells [1–3]. The corresponding physiological role of such fluctuations remains unclear. Contrary to expectations, recent experiments have shown that fluctuations of nuclear components (eg. membrane or DNA loci) are not governed by intra-nuclear activity, but rather by the cytoplasmic acto-myosin contractility [4–6]. In this Letter, we introduce a simple model based on active gel theory [7–9] which illustrates how variation of contractility can induce a maximum in the fluctuation spectrum of the nuclear shape. Though our focus here is on cell nucleus fluctuations, our findings are also applicable to many other situations in which an active gel drives fluctuations of an inclusion, in particular at the scale of tissues.

In a variety of cell types and under different external conditions, the nucleus and its components (membrane, DNA loci) have been observed to undergo fluctuations that are too large to be accounted by thermal fluctuations, but rather originate from the active remodeling of contractile actomyosin within the cytoplasm [10, 11]. Stresses are transmitted across the nuclear membrane through physical links connecting the actomyosin and lamin meshworks. The large scale architecture and activity of the cytoskeleton may be modulated by geometrical confinement: for instance, cells confined within small circular domains display shorter actomyosin structures and softer nuclei than those on large rectangular domains [5, 12]. Here, we focus on the rather unexpected experimental result of Ref. [5] which, combining drug treatments and geometric constraints, shows that the nuclear area fluctuations are maximal for an intermediate level of contractility (see Fig. 2a.). Indeed, treatment by Cytochalasin-D – an actin depolymerizing agent – reduces the amplitude of nuclear fluctuations in cells placed on small circular patches (ie. with low level of contractile filamentous actin) while the same drug increases nuclear fluctuations in cells on large rectangular patches (ie. with

a high level of contractile filamentous actin).

We describe the dynamics of an inclusion subject to stress fluctuations arising from the surrounding actomyosin fluid confined within $x \in [-L, L]$ (for simplicity, we consider a one dimensional situation). We successively investigate the cases of a rigid inclusion (eg. a stiff nucleus) and of an elastic inclusion (eg. soft nucleus) that is embedded in a confined active gel of fluctuating activity; further geometries will be considered in a following paper [13]. We find that, in a non-equilibrium situation, stress fluctuations generate an effective attraction towards the edges of the confining domain, which is reminiscent of Casimir forces [14, 15]. We then show that fluctuations are maximal when the fluctuation-induced attraction is balanced by a centering force induced by the contractility of the apical cortex. This suggests that the mean contractility of the apical cortex tends to focus the nucleus at the center of the cell, while contractility fluctuations have the opposite effect. We predict the existence of an optimal active stress level that maximizes the amplitude of the inclusion fluctuations, providing a rationale for the unexpected experimental results of [5].

Here, we propose an original model for the active stress fluctuations felt by the inclusion (whether rigid or elastic). Following [7, 9] and integrating over the cortex area in the directions transverse to x (see SM [16]), we find that the tension $\sigma_{\text{tot}}(x, t)$ along the gel coordinate x reads:

$$\sigma_{\text{tot}}(x, t) = \eta \partial_x v(x, t) + \zeta \Delta \mu + \theta_T + \theta_A, \quad (1)$$

where η is an effective one dimensional viscosity and $v(x)$ is the gel velocity; $\zeta \Delta \mu$ models the medium activity, e.g. the tension generated by contractile motors; θ_T and θ_A are fluctuating tensions of thermal and active origins, respectively. We expect those active fluctuations to result from fluctuations in the width and height of the cortex in the transverse directions to x (see SM [16]). We assume that these noise sources are mutually independent and spatially uncorrelated. Note that in Eq. (1), we consider a constant viscosity. As a consequence of the fluctuation-

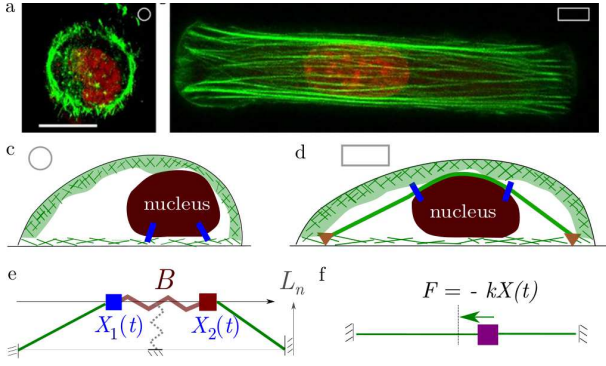


Figure 1: (a, b) Projected intensity of actin (phalloidin labelling) and of the nucleus (DAPI labelling) of cells placed on (a) circular and (b) rectangular patches of fibronectin (Scale bar: $10\mu\text{m}$). (c, d) Schematic representation of the cortex (green) within cells placed on patches either (c) circular ($500\mu\text{m}^2$) or (d) rectangular ($1800\mu\text{m}^2$). Physical links (blue and red) connect the nucleus (grey) to the actin mesh-work (green). In (d), the nucleus is compressed by actin fibers (solid green line) anchored to the substrate through focal adhesions (brown triangles). (e-f) Models considered here, with (e) a restoring force provided by the geometry of the active segments on an elastic inclusion maintained at a distance from the base and (f) a linear restoring force on a rigid inclusion.

dissipation theorem, the thermal noise θ_T is to be considered as delta-correlated in time [17, 18]. In contrast, we assume that the active noise θ_A displays significant time correlation, which we choose to be exponential: $\langle \theta_A(x, t) \theta_A(x', t') \rangle = 2\Lambda_A \delta(x - x') \exp(-|t - t'|/\tau_A)/\tau_A$. Similar assumptions on the active noise have been introduced to study the diffusion of DNA loci in the presence of intra-nuclear remodeling processes [19–21]. Here, we expect Λ_A to be related to the motor activity [22] and that $\tau_A \approx 60\text{s}$ corresponds to a typical remodeling time of the apical actin [23].

We now consider a rigid inclusion at the position X_t . At the cell scale, low Reynolds number holds and forces should be balanced at any time step. In the absence of external friction, this implies that tension should be constant in both segments to the left and right of the inclusion, e.g. $\sigma_{\text{tot}}(x, t) = \sigma_{\text{tot}}^{(L)}(t)$ for $x \in [-L, X(t)]$ (conversely $\sigma^{(R)}$ on the right). The existence of a fluctuating gel velocity field leads (by continuity) to the random motion of the inclusion. Integration of Eq. (1) over the segment $[-L, X(t)]$ leads to:

$$\sigma_{\text{tot}}^{(L)}(t) = \frac{\eta}{L + X_t} \dot{X}_t + \zeta \Delta\mu + \frac{\int_{-L}^{X_t} dx' \theta_A}{L + X_t}, \quad (2)$$

where we assumed a zero velocity on the edge $-L$; a similar equation to 2 holds on $\sigma^{(R)}$. We then determine \dot{X}_t in the limit of a short correlation time $\theta_A \ll t_u$, where $t_u = (\eta^2 L)/(2\Lambda_A)$ is to be interpreted as a characteristic displacement time of the inclusion; this allows to consider the active noise θ_A as delta-correlated with Eq. (2). We

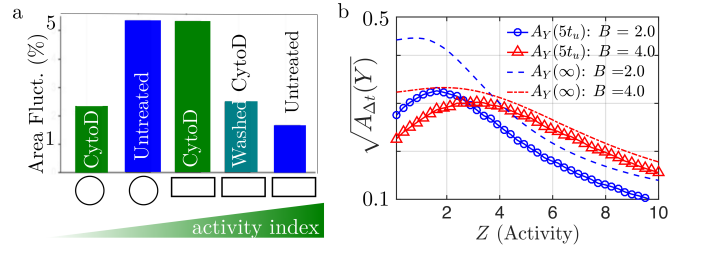


Figure 2: (a) Nuclear area fluctuations in terms of an activity index – both the actin concentration (measured by phalloidin) and the number of myosin bound to actin (measured by the level of phosphorylated myosin light chain) are increasing from left to right (excerpt from [5]). (b) Variation of the fluctuations in the width of an elastic inclusion (defined in Eq. (7)) as a function of the cortical activity parameter Z , for two values of the normalized nuclear elasticity $B = 2$ and $B = 3$. The observation time $\Delta t = 5t_u = 2 \cdot 10^3\text{s}$ is comparable to the duration of experiments in [5] (see SI [16]). We model the effect of the actin-disruption drug Cytochalasin-D as a reduction in the normalized activity Z .

find that

$$\dot{X}_t = \Gamma(X_t) f + g_A(X_t) \Theta_A, \quad (3)$$

where $\Gamma(x) = (L^2 - x^2)/(2\eta L)$ and

$$g_A^2(x) = \frac{2\Lambda_A}{\eta^2 L} (L^2 - x^2), \quad (4)$$

where Θ_A is a standard Gaussian white noise. Spatially varying friction is a characteristic feature of systems breaking translational invariance [25, 26]. In contrast to the standard Langevin equation, the noise in Eq. (3) depends on the outcome of \dot{x}_t ; such multiplicative noise takes a well-defined meaning only with a particular definition of the variance of the noise, called convention. Here, the Stratonovich convention applies, since it can be shown to correspond to the adiabatic elimination of the active noise correlation time τ_A [24]. The Fokker-Planck equation associated to the Stratonovich Eq. (3) reads

$$\partial_t P = -\partial_x \left\{ \Gamma(x) f(x) P + \frac{g_A}{2} \partial_x [g_A P] \right\}. \quad (5)$$

Notice that the steady-state distribution of 5 does not follow the Boltzmann statistics, which is to be expected since the active noise does not satisfy the fluctuation-dissipation theorem.

We first apply Eq. (3) in the case of a harmonic restoring force $f(x) = -Kx$; additionally, we assume a constant friction $\Gamma(x) = L/(2\eta)$ for illustration purposes (see [16] for the complete case). In this case, the stationary probability distribution reads

$$P(x) = \frac{\sqrt{\pi} \Gamma(k + \frac{1}{2})}{L \Gamma(k + 1)} (1 - (x/L)^2)^{-1/2+k}. \quad (6)$$

where $k = (KL^2\eta)/(4\Lambda_A)$ is a characteristic time scale that normalizes the variance of the noise term, From Eq. (6), we observe a significant change in the shape of the probability distribution at $k = k_c = 1/2$. For large restoring forces $k > 1/2$, the inclusion is localized around the center. In contrast, for small restoring forces $k < 1/2$ the probability distribution diverges on the edges, indicating the inclusion is attracted by the boundaries (see Fig. 3). This divergence can be traced back to the zero-velocity boundary condition at the edges, which leads to the cancellation of both the friction function and of the fluctuations intensity there (see Eq. (4)). At $k = 1/2$ the probability distribution is uniform, which corresponds to the Boltzmann distribution in the absence of applied force; indeed, in that case, the elastic restoring force is equal to the counter-term $g_A \partial_x g_A / 2$ associated with the Hanggi-Klimontovich convention [26, 27].

Finite-time variance Even though the shape of the probability distribution undergoes a dramatic change at $k = k_c$, we find that the variance of the inclusion position exhibits no singularity as a function of k (which is a common feature of systems in zero dimension [28]) but rather decreases monotonically as $1/k$. Here, we show that fluctuations measured on sufficiently short finite-time windows Δt are maximal at an optimal restoring force parameter k_{opt} close to the value of k_c . The observation time scale Δt is to be compared to both (i) a long time scale related to the time required for the inclusion to switch from one edge to the other (for a weak restoring force: $t_0 \approx 10t_u$ [16]) and (ii) to a short time scale related to its fluctuations in the vicinity of a given edge. The existence of an optimum in the amplitude fluctuations is visible at the level of individual trajectories, see Fig. 3a. At $k = k_c$, the trajectory exploration over $\Delta t = t_u$ is large compared to the cases of a weak (resp. strong) restoring forces, in which the inclusion is localized at one of the edges (resp. at the center).

To obtain a more quantitative statement, we define the following measure of the amplitude of fluctuations, called finite-time variance:

$$A_{\Delta t}(X) = \langle (X - \bar{X}_{\Delta t})^2 \rangle_s, \quad (7)$$

where $\bar{X}_{\Delta t}(t)$ is the running average position over the time window Δt : $\bar{X}_{\Delta t}(t) = (1/N) \sum_{i \in [1, N]} X(t + i\Delta t/N)$, and $\langle \cdot \rangle_s$ refers to an average over the stationary distribution. For $\Delta t \ll t_0$, we find that $A_{\Delta t}$ exhibits a maximum at an optimal restoring force parameter k_{opt} close to k_c (see SM [16]). For a long observation window $\Delta t \gg t_0$ there is no optimal restoring force, since the finite-time variance converges to $\text{Var}(X_t)$, which decreases monotonically with k .

Geometry-induced centering As visible on Fig. 1b, cells placed on rectangular patches display actin fibers on top of the nucleus that compress it vertically. We model the nucleus as an elastic inclusion under a contractile

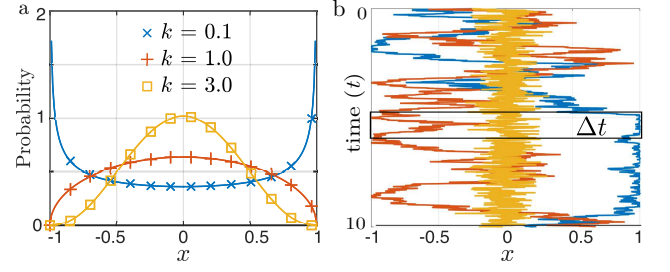


Figure 3: (a) Spatial probability distribution corresponding to Eq. (6) for different normalized strength of the restoring force $k = 0.1$ (blue), $k = 1$ (red) and $k = 3$ (orange). (b) Three typical trajectories. For $k = 0.1$ (blue), the inclusion is confined to the edges, while for a large restoring force $k = 3$ (orange), it is confined to the center. For $k = 1$ (red), the particle exhibits the largest displacements over the observation time Δt .

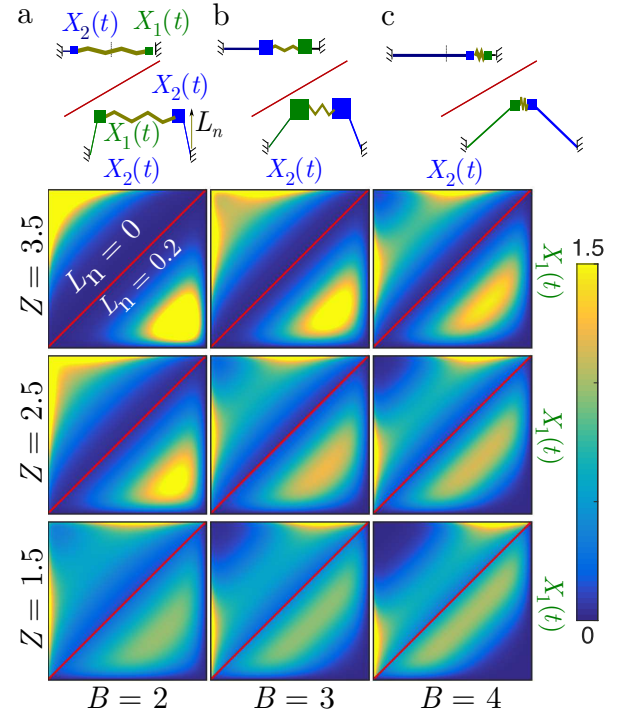


Figure 4: (a-c) Sketch of the most probable configuration of an elastic inclusion between two active gel segments, with increasing elastic modulus from (a) to (c). The higher panel corresponds to $L_n = 0$ and the lower panel to $L_n = 0.2$. (d) Probability map $P(X_1, X_2)$ as a function of both the active stress Z (top to bottom rows: $Z = 1.5, 2.5, 3.5$) and of the elastic modulus B (left to right columns: $B = 2, 3, 4$).

compressive loading.

We assume that that two ends of the inclusion are constrained to remain at a fixed height $z = L_n$ (as justified in SI). Mechanical equilibrium requires the identity of the projected tensions: $\sigma_L(1 + X_1)/l_t = \sigma_R(1 - X_2)/r_t = B(X_2 - X_1)$, where X_i are the coordinates of the two edges of the inclusion (in cell length L units) while

$l = \sqrt{(1+X_1)^2 + L_n^2}$ and $r = \sqrt{(1-X_2)^2 + L_n^2}$ are the left and right lengths of the actin fibers (see Fig. 1d). Applying the same method as in our first calculation, we find that the dynamics of $\mathbf{X}_t = (X_1, X_2)$ reads $\dot{\mathbf{X}} = \mathbf{A} + \mathbf{D} \cdot \Theta_A$,

$$\mathbf{A} = \begin{bmatrix} \frac{B(X_2 - X_1)l^3}{(1+X_1)^2} - \frac{Zl^2}{1+X_1} \\ \frac{B(X_1 - X_2)r^3}{(1-X_2)^2} + \frac{Zr^2}{1-X_2} \end{bmatrix}, \mathbf{D} = \begin{bmatrix} \frac{l^{3/2}}{1+X_1} & 0 \\ 0 & \frac{r^{3/2}}{1-X_2} \end{bmatrix}, \quad (8)$$

where (i) time is expressed in units of t_u , (ii) $B = ELt_u/\eta$ is a normalized elastic modulus, (iii) $Z = \zeta\Delta\mu t_u/\eta$, where $\zeta\Delta\mu$ is a normalized cortex activity and (iv) $\Theta_A = (\Theta_1, \Theta_2)$ is an uncorrelated Gaussian white noise vector with $\langle \Theta_i(t)\Theta_j(t') \rangle = \delta_{ij}\delta(t-t')$.

As previously explained, we interpret Eq. (8) in the Stratonovich convention under which the Fokker-Planck equation reads: $\partial_t P = \partial_i (A_i P + D_{ii} \partial_i D_i P)$, with a summation over $i = 1, 2$. Following [24], we derive two equations on the derivatives $\partial_i \ln P$ and we find that the stationary probability distribution reads:

$$P(x_1, x_2) = \frac{N (l_t r_t)^{3/2} e^{-B(x_2 - x_1)^2 - 2Z(l_t + r_t)}}{(1 - x_2)(1 + x_1)}, \quad (9)$$

where N is a normalization constant (see derivation in SM [16]). Similarly to Eq. (6), the distribution $P(x_1, x_2)$ is flattened at intermediate values of the parameters (B, Z) (as visible in Fig. 4d). Therefore, following the argument presented in Fig. 4, we expect fluctuations to be maximal for an intermediate values of (B, Z) .

As a proxy for the nuclear area, we consider the length of the inclusion $Y = X_2 - X_1$. We evaluate $A_{\Delta t}(Y)$ by Monte-Carlo sampling and we find that, for any given value of B and L_n , $A_{\Delta t}(Y)$ is maximal for an optimal activity Z_{opt} – and this even for remarkably large values of the observation window $\Delta t = 5t_u \approx 10^3$ s. Simulations further indicate the following approximate relation for the optimal activity maximizing $A_{\Delta t}(Y)$: $Z_{\text{opt}} = \alpha_1 B + \alpha_2 L_n^2 + \alpha_3$, where both α_1 and α_2 are positive (see Fig. 5). The finite time variance at optimality is an increasing function of both the elastic strength B and of the nucleus height L_n ; the latter modulates the contribution of the cortical activity to the centering force (see Fig. 5b).

Comparison to experiments Our theoretical model rationalizes the counter-intuitive experimental observation that actin polymerization can either reduce or increase the amplitude of fluctuations (Fig. 1a). We show that by continuously varying the parameters – such as the restoring force or contractility – we can reproduce the observation of a maximum in the amplitude of fluctuations (either in inclusion position or size). Thus, the same biochemical perturbation can induce opposite behavior depending on the position of the starting point relative to the maximum. More precisely, the experiment done on rectangular patches with untreated cells correspond to a point on the theoretical curve that is on

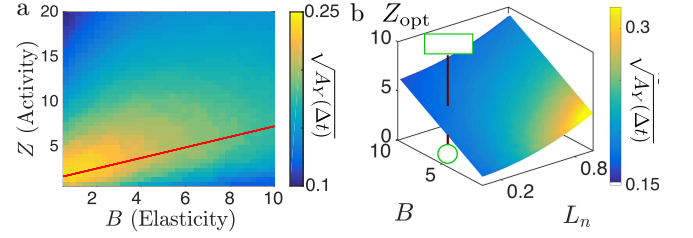


Figure 5: (a) Finite-time variance on the width of an elastic inclusion $A_{\Delta t}(Y)$ in the elastic modulus/activity plane, as evaluated over a time-window $\Delta t = 5t_u$ and for a height $L_n = 0.50L$; the red line indicates a linear fit of the locus of optimal activity. (b) Surface of the optimal activity level Z_{opt} , colored by the value the maximal $\sqrt{A_{\Delta t}(Y)}$. The vertical red line corresponds to the set of parameters used in Fig. 1b, with a higher activity for a rectangular confinement than for a circular one.

the right of the maximum (see Fig. 2). Thus reducing the restoring force by adding CytoD or blebbistatin increases fluctuations [5]. In addition and in agreement with our argument, treatment by jasplakinolide – which increases the actin level – further decreases fluctuations. Conversely, the case of untreated cells on circular patches corresponds to a point close to the maximum (see Fig. 2a); in this case, CytoD treatment drives the cell to the left of the maximum and decreases fluctuations. We illustrate this argument on Fig. 5b, where we represent the surface of optimal activity maximizing $A_{\Delta t}(Y)$ in a two-dimensional nuclear elastic strength and height plane.

Estimated values for the parameters further support our model findings. We find that $B = 1$ corresponds to a nuclear elastic modulus value $E = 50$ Pa and that $Z = 10$ leads to an active stress term $\zeta\Delta\mu_b = 5 \cdot 10^2$ Pa, which are both in agreement with previously reported values [29, 30] (see SM [16]).

Conclusion In this Letter, we show that the incorporation of an out-of-equilibrium fluctuating noise in generalized hydrodynamics equations leads to an attraction of a confined inclusion to the boundaries. This attraction, which is reminiscent of a Casimir effect, explains the experimental observations on the nuclear area fluctuations from Ref. [31]. Moreover, taking into account such effect is potentially crucial to properly assess forces in biological materials. We expect such fluctuation-induced force to arise not only at the cell scale, but also at the sub-nuclear levels, potentially affecting rheological studies based on the tracking of inclusions within such material [11, 26]. Eventually, our work provides an adapted framework to include active fluctuations in tissues modeled as networks of active gel segments.

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